UNITED STATES ENVIRONMENTAL PROTECTION AGENCY WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

OFFICE OF PESTICIDE PROGRAMS REGISTRATION DIVISION (7505P)

DATE: 08/27/12

SUBJECT: Product Chemistry Review of "1-Naphthylacetic Acid Technical" TGAI/MUP

FROM: Indira Gairola Product Chemistry Team
Technical Review Branch / Registration Division (7505P)

TO: Rosemary Kearns / Tony Kish, PM 22
Fungicide Branch / Registration Division (7505P)"

08/28/12

8/29/12

DP BARCODE: 398571
DECISION NO.: 459562
REGISTRATION NO./ FILE SYMBOL NO.: 73049-UIO
PRODUCT NAME; 1-Naphthylacetic Acid Technical
PC CODE: 056002
REGISTRANT: Valent Biosciences Corporation
USE: Plant growth regulator
FOOD USE: Yes [X] No [ ]
MRID NUMBERS: 487134-01 through -04

INTRODUCTION:

The applicant submitted an application for approval of the new manufacturing use product "1-Naphthylacetic Acid Technical." In support of the application, the applicant submitted Group A product chemistry data with MRID Nos. 487134-01 through 487134-03 and Group B product chemistry data with MRID No. 487134-04. The CSF (dated 12/26/2011) for the basic formulation was also submitted for the product.
The Primary review was done by Summitec Corporation, 9724 Kingston Pike, Suite 602 Knoxville, Tennessee Task Order No. 3-A-11.
TRB has been asked to determine the acceptability of the product chemistry data and basic CSF dated 12/26/11.

SUMMARY OF FINDINGS:

1. Group A guidelines:

830.1550 (product identity & composition)

The active ingredient was adequately described (MRID 487134-01). The nominal concentration of the active ingredient (99.0%, from CSF dated 12/26/11 Page 8 in MRID 487134-01) matches that on the product label and is close to the average derived from the 5-batch preliminary analysis (99.22%, from Page 14 in MRID 487134-02). However, the name of the active ingredient should be "1-Naphthylacetic acid," not "1-Naphthaleneacetic acid, sodium salt" as indicated on the product label. Applicant is required to correct the label ingredient statement. The chemical name for one impurity is [redacted] not [redacted] as indicated on the CSF. This needs to be corrected .

830.1600 (description of materials used to produce the product)

The submitted data are acceptable. MSDSs of all the starting materials, and their suppliers and specifications are provided in the study (MRID 487134-01). The information presented meets the data requirements for 40 CFR 158.160.

830.1620 (description of production process)

The submitted data are not completely acceptable. Description of the production process, chemical pathway, and a flow chart were provided in MRID 487134-01. However, no information was provided for quality control. The information presented does not meet the data requirements for 40 CFR 158.162.

830.1670 (discussion on the formation of impurities)

The submitted data are acceptable (MRID 487134-01). Four potential impurities were identified and quantified as part of the five-batch analysis (MRID 487134-02 and 487134-03). The information presented meets the data requirements for 40 CFR 158.167.

830.1700 (preliminary analysis)

The submitted data are acceptable. Results are presented for a five-batch analysis (MRID 487134-02 and 487134-03) using HPLC-UV with internal standard calibration for the A.I. The nominal concentrations of the A.I. were: 99.73, 99.65, 98.92, 99.55 and 98.25% (average 99.22%, from Page 14 in MRID 487134-02). The information presented meets the data requirements for 40 CFR 158.170.

830.1750 (certified limits)

The nominal concentration for the A.I. was established based on the average value from the five-batch analysis. The lower certified limit for the A.I. is out of EPA's Standard Certified Limits.

830.1800 (enforcement analytical method)

The submitted data are acceptable. The analytical method for quantifying the A.I. is HPLC-UV using internal standard calibration. The method was validated for specificity, linearity, repeatability, accuracy and precision (MRID 487134-02 and 487134-03). The information presented meets the data requirements for 40 CFR 158.180.

2. Group B guidelines (physical-chemical properties):

The registrant submitted data for color, physical state, odor, UV/visible absorption and dissociation constants (MRID 487134-04). No experimental data were provided for 830 series group B guidelines for stability to normal and elevated temperatures/metals/metal ions, oxidation/reduction, flammability, explodability, storage stability, miscibility, corrosion characteristics, pH, viscosity, melting point, boiling point, bulk density, partition coefficient, miscibility, water solubility and vapor pressure. The Data Matrix table indicates that data are available for all these endpoints, except for miscibility, viscosity and boiling point.

CONCLUSIONS:

The TRB has reviewed the product chemistry data submitted for Technical MUP (produced by Valent Biosciences Corporation) and has concluded that:

1. The product chemistry data submitted corresponding to guidelines 830.1550 (product identity and composition), 830.1600 (description of materials used to produce the product), 830.1670 (discussion of the formation of impurities), 830.1700 (preliminary analysis) and 830.1800 (enforcement analytical method) are acceptable. Applicant is required to correct the label ingredient statement. (see summary of findings Item 1. The product chemistry data submitted corresponding to guideline 830.1620 (description of the production process) are not acceptable. No quality control information was provided.

2. The product chemistry data submitted corresponding to guideline 830.1750 (certified limits) are not acceptable. The lower certified limit for the A.I. is out of the range of the guideline OCSPP 830.1750 recommendation.

3. The proposed basic CSF is unacceptable on account of the following reasons :

a) Name of the active ingredient is incorrect , correction of label ingredient statement is required

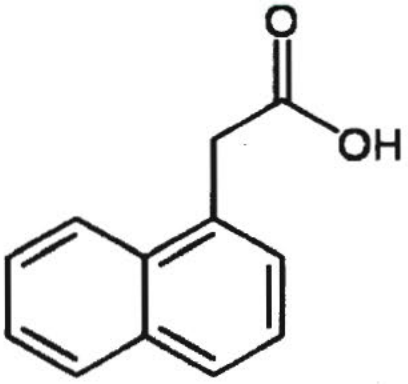
b) The letter "h" is missing in "Naphtyla" which is a part of the names for the product, active ingredient and [redacted] impurities. The chemical name for one impurity is [redacted] not [redacted] as indicated on the CSF. This needs to be corrected. The CAS number of the A. I. was not given on the CSF.

c) The lower certified limit for the A.I. is out of the range of the guideline OCSPP 830.1750 recommendation and not in compliance with with 40 CFR 158.350.

d) No information was provided for Density and pH on the CSF.

830.1550. Product identity & composition: (MRID No. 487134-01)

Common Name: 1-Naphthylacetic acid
Chemical name (CAS): 1-Naphthaleneacetic acid
(IUPAC): 1-Naphthylacetic acid CAS No.: 86-87-3
PC Code No.: 056002
Empirical Formula: $C_{12}H_{10}O_2$
Molecular Weight: 186.20 g/mole
Structural Formula:



830 Series Subgroup A (Product identity & composition)

Table 1. Manufacturing and Impurity Data for Technical TGAI "1-Naphthylacetic Acid Technical."

GLN	Requirement	MRID	Status	Details and/or Deficiency
830.1550	Product Identity & Composition	487134-01	U	Needs upgrading
830.1600	Description of materials used to produce the product	487134-01	A	MSDSs of the starting materials, and their suppliers and specifications were provided in MRID 487134-01.
830.1620	Description of production process	487134-01	U	No quality control information was provided.
830.1670	Discussion on the formation of impurities	487134-01	A	The potential impurities were identified and quantified.
830.1700	Preliminary analysis	487134-02, 487134-03	A	Five-batch analyses of the A.I. by HPLC-UV
830.1750	Certified limits	487134-01	N	The lower certified limit for the A.I. is out of EPA's Standard Certified Limits.
830.1800	Enforcement analytical method	487134-01	A	HPLC-UV

A = Acceptable; N = Unacceptable (see Deficiency); N/A = Not Applicable; G = Data gap; I = In progress; U = Up-grade (additional information required);

830 Series Subgroup B (Physical-Chemical Properties)

Table 2: Physical and Chemical Properties of: Technical TGAI "1-Naphthylacetic Acid Technical."

GLN	Requirement	MRID	Status	Result or Deficiency
830.6302	Color	487134-04	A	White
830.6303	Physical state	487134-04	A	Powder
830.6304	Odor	487134-04	A	No characteristic odor
830.6313	Stability to normal and elevated temperatures, metals, and metal ions	405230-03	A	Cited MRID # 405230-03
830.6314	Oxidation/reduction: chemical incompatibility	441696-02	A	Cited MRID # 405230-03
830.6315	Flammability	CSF (dated 12/26/2011)	NA	Not applicable
830.6316	Explodability	441696-02		Cited MRID # 405230-03
830.6317	Storage stability	435804-01 441006-02	U	No data provided*
830.6319	Miscibility			
830.6320	Corrosion characteristics	441006-01 441006-02	U	No data provided*
830.7000	pH	405230-03	A	Cited MRID # 405230-03
830.7050	UV/Visible absorption	487134-04	A	Characteristic spectra were obtained under neutral, acidic and alkaline conditions in methanol. Refer to MRID 487134-04 for results.
830.7100	Viscosity		NA	
830.7200	Melting point	405230-03	A	Cited MRID # 405230-03
830.7220	Boiling point		NA	
830.7300	Density	405230-03	A	Cited MRID # 405230-03
830.7370	Dissociation constants in water (DC)	487134-04	A	pKa = 4.23
830.7550	Partition coefficient	405230-03		Cited MRID # 405230-03
830.7840	Water solubility	405230-03	A	Cited MRID # 405230-03
830.7950	Vapor pressure	405230-03		Cited MRID # 405230-03

A = Acceptable; N = unacceptable (see Deficiency); N/A = Not Applicable; G = Data gap; I = In progress ; U = Up-grade (additional information required); W = waivers

*The Data Matrix table indicates that data are available for all these endpoints (except for miscibility, viscosity and boiling point) and were submitted by a company other than the current submitter.

830.1800 (enforcement analytical method)

The analytical method employed to quantify the active ingredient is HPLC-UV using internal standard calibration. The method was validated for specificity, linearity, repeatability, accuracy and precision (MRID 487134-02 and 487134-03).

[redacted]

The registrant provided the following information for quantifying the active ingredient (MRID 487134-01).

Analytical Method of 1-Naphthylacetic Acid TGAI

The analytical methodology for the assay for the active ingredient 1-Naphthylacetic Acid TGAI was validated and implemented to fulfill the requirements of OPPTS Guidelines 830.1700, 830.1800, Directive 91/414EEC as amended by Directive 94/37/EC, PMRA Regulatory Directive Dir 98-04 and APVMA Agricultural Requirements Part 2 for the analytical profile of batches. The general conditions for chromatographic analysis are from Nufarm S.A.S. method: C-Organique-00460-C-TA, part A. as follows:

HPLC Parameters

Column:	Chromcart Nucleosil 100, C18 AB, 125 x 4 mm, 5 µm, Macherey-Nagel Reg.No. 721623.40 coupled with a pre-column: Nucleosil 100, C18 AB, 8 x 3 mm, 5 µm, Macherey-Nagel Reg.No. 721603.30.
Mobile Phase:	75% of buffer solution (shown below) 25% of Acetonitrile
Flow rate:	1 mL/min
Temperature:	27°C
Wavelength:	220 nm
Injection volume:	5 µL
Analysis Time:	25 min
Retention times:	2.3 min Acetanilide, (Internal Standard) 11.3 min 1-Naphthyl acetic acid
Preparation of buffer:	2.64 g of Ammonium Phosphate Dibasic, $(NH_4)_2HPO_4$, is weighed and transferred to a 2-L volumetric flask filled with 1.5 L of HPLC grade water. The pH of the solution is then adjusted to 2.60 (±0.02) with phosphoric acid and then filled with water to the mark. The flask is inverted 20 times to assure proper mixing.

Preparation of Internal Standard solution:

Weigh accurately 1.0 g of acetanilide into a 1 L volumetric flask and fill to the mark with HPLC grade methanol. Invert to assure complete dissolution.

Preparation of Stock Reference Solution:

Into a 50 mL volumetric flask accurately weigh approximately 120 mg (to the nearest 0.01 mg) of 1-Naphthylacetic Acid. Add methanol to mark and invert to assure complete dissolution.

Preparation of Calibration solution:

120 mg of 1-Naphthylacetic Acid reference standard is weighed into a 100 mL volumetric flask. 5 mL of Stock Reference Solution is added by pipette and 20 mL of Internal Standard solution is added by pipette. The flask is brought to mark with methanol and inverted to assure complete dissolution.

Preparation of Sample solution:

Into a 50 mL volumetric flask accurately weigh approximately 120 mg (to the nearest 0.01 mg). Add methanol to the mark and invert to assure complete dissolution. Pipette 5 ml of this solution and pipette 20 mL of Internal Standard solution into a 100 mL volumetric flask and fill to the mark with methanol. Invert to assure complete dissolution.

Accuracy RSD:	0.23
Precision RSD:	0.66
Repeatability RSD:	0.28
Linearity range (mg/mL):	0.06 – 0.18 (r=0.9999)

Confidential appendix

830.1600 (description of materials used to produce the product)

[redacted]

830.1620 (description of production process)

The registrant provided the following information for this guideline (MRID 487134-01). No information for quality control was provided.

Manufacturing process information may be entitled to confidential treatment

Pages 10-16 Manufacturing process information may be entitled to confidential treatment

The nominal concentration for the active ingredient was established based on the average of the values from the five-batch preliminary analysis (from Page 14 of MRID 487134-02). The certified lower limit of the A.I. is out of the range of the guideline OCSPP 830.1750 recommendation.
A copy of the basic CSF dated 12/26/2011 is shown below.